Docket No.: 066661-0021 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	Customer Number: 41552
Hood and Siegel	:	Confirmation Number: 7808
Serial No.: 09/724,898	:	Group Art Unit: 1631
Filed: November 28, 2000	:	Examiner: Mary K. Zeman

For: MULTIPARAMETER ANALYSIS FOR PREDICTIVE MEDICINE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION PURSUANT TO 37 C.F.R. § 1.132

We, Leroy Hood and Andrew F. Siegel, declare as follows:

1) We are the Leroy Hood and Andrew F. Siegel named as co-inventors of the above-identified application.

2) I understand that the claims under examination stand rejected, in part, as allegedly anticipated by Friend et al., U.S. Patent No. 6,324,479 (hereinafter Friend et al. '479) and Friend et al., US 2001/0018182 (hereinafter Friend et al. '182).

3) The claimed methods of determining a comparative expression profile and diagnosing a health state are distinct from Friend et al. '479 and Friend et al. '182. The methods described in Friend et al. '479 and '182 are all based on a specific form (interpolation) of unidimensional analysis, in contrast to the multidimensional analysis of the claimed methods.

4) The interpolated response curves of Friend et al. '479 and '182 are unidimensional functions (meaning univariate functions, or functions of a single variable), as is made

clear throughout the specification and claims of Friend et al. '479 and '182. Each such unidimensional function is for a single cellular constituent, describing how it responds to the perturbation level. For example, Figure 4 in Friend et al. '479 and Figure 3 in Friend et al. '182 show a unidimensional parameterized function for the singular cellular constituent YOL031C. In column 14, lines 51-53, of Friend et al '479 and page 8, paragraph 78, lines 6-7, of Friend et al. '182, it is stated that "This interpolation method is preferably accomplished either by spline fitting or by model-fitting." For spline fitting, unidimensional methods are shown from column 14, line 56, through column 15, line 6, of Friend et al. '479 and page 8, paragraphs 79 through 80 of Friend et al. '182. Note that Equation 1 (column 14 of Friend et al. '479 and page 8, column 2, of Friend et al. '182) applies only to the *k*th cellular constituent. For model fitting, unidimensional methods are shown in column 15, lines 7-38, of Friend et al. '479 and pages 8-9, paragraphs 81 through 83, of Friend et al. '182, resulting in one interpolated unidimensional function per cellular constituent. "In model fitting, the perturbation responses are interpolated by approximating each by a single parameterized function" (column 15, lines 7-9, of Friend et al. '479 and page 8, paragraph 81, lines 1-3, of Friend et al. '182). These unidimensional interpolation functions are then used throughout the section on Expression Profile Representation (column 13, line 65, through column 16, line 60, of Friend et al. '479 and page 8, paragraph 73, through page 9, paragraph 90, of Friend et al. '182) in order to identify the best-fitting perturbation level with respect to multiple cellular constituents, using the univariate interpolated response curve for each one. Thus, both Friend et al. '479 and '182 use interpolated response profiles extracted from interpolated response curves for analysis of expression profiles.

5) In contrast to Friend et al. '479 and '182, the claimed methods are fully multidimensional. The claims recite the phrase "reference expression region." A region, as used in this context, is defined as "a region of multidimensional space classified using one or more statistical methods" (specification page 19, line 28, through page 20, line 1). Exemplary statistical methods are listed in the specification (page 20, lines 6-19; page 40, line 19, through page 44, line 21) and examples are given (pages 128-137).

6) To see that important information can be irretrievably lost when interpolated response curves are used as proposed by Friend et al. '479 and '182, but that this information is retained and used by the claimed multidimensional methods, consider a hypothetical example with two molecules or cellular constituents (see Exhibit A). In this example, the interpolated response curve for each of the molecules is flat when using the methods of Friend et al. '479 and '182, reflecting no change with respect to the perturbation. However, the use of the claimed multidimensional methods, for example, multivariate classification theory as described in Example I (pages 128-131), allows us to separate the perturbed from the unperturbed samples.

7) In the example illustrated in Exhibit A, there are two perturbation levels, and the mean response for each molecule is the same for each of the perturbation levels. For the data shown in the figure (Exhibit A) , the mean level for molecule 1 is -0.289 for perturbation level 0 and is the same -0.289 for the sample corresponding to perturbation level 1. For molecule 2, the mean level is 0.401 for perturbation level 0 and the same 0.401 for perturbation level 1. Such a response might happen if normal unperturbed individuals (perturbation level 0) show higher levels of molecule 1 only when molecule 2 is expressed at a high level. In perturbation level 1, it might be that the regulatory mechanism has been disrupted, allowing each molecule to be expressed at an intermediate level.

8) The interpolation methods of Friend et al. '479 and '182 cannot distinguish these two perturbation levels (see Exhibit B). Note that the interpolated response curve for molecule 1 is a horizontal line because the mean response does not change with the perturbation level (this is true for either spline or model fitting). Similarly, the interpolated response curve for molecule 2 is also a horizontal line. Equation 3 of Friend et al. (column 15 of '479 and page 9, column 1, of '182) cannot find the "best-fit over all possible values" (column 15, lines 48-49, of '479 and page 9, paragraph 85, lines 4-5, of '182) of the perturbation level for a given diagnostic expression profile *D* because Equation 3 will have the same numeric value for both perturbation levels. Information has been irretrievably lost through the use of interpolation response profiles extracted from interpolation response curves.

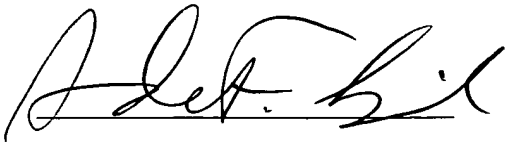
9) In contrast to Friend et al. '479 and '182, the claimed multidimensional methods can successfully separate and classify the perturbation levels in this example because the methods work directly with response regions in multidimensional space. Using two-dimensional response regions, the two perturbation levels can easily be separated by any of a variety of methods (see Exhibit A). Visualizations of two-dimensional response regions produced with various methods are exemplified in Figures 3-5, corresponding to Examples I-III (pages 128-137).

10) In conclusion, I believe that the claimed methods are substantially different from those of Friend et al. '479 and '182 As discussed above, there are substantive differences between the claimed methods and those described in Friend et al. '479 and '182. An example is described above of a situation in which multidimensional analysis, such as in the claimed methods, is necessary in order to correctly classify individuals, whereas the methods of Friend et al. '479 and '182 are unable to separate the perturbation levels. Therefore, I believe that the claimed methods are distinct from Friend et al. '479 and Friend et al. '182.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that any such willful false statement may jeopardize the validity of the application or any patent issued thereon.

7/27/04 — Leroy Hood

Date — Signature — Leroy Hood, M.D., Ph.D.

7/23/04 — 

Date — Signature — Andrew F. Siegel, Ph.D.

Exhibit A

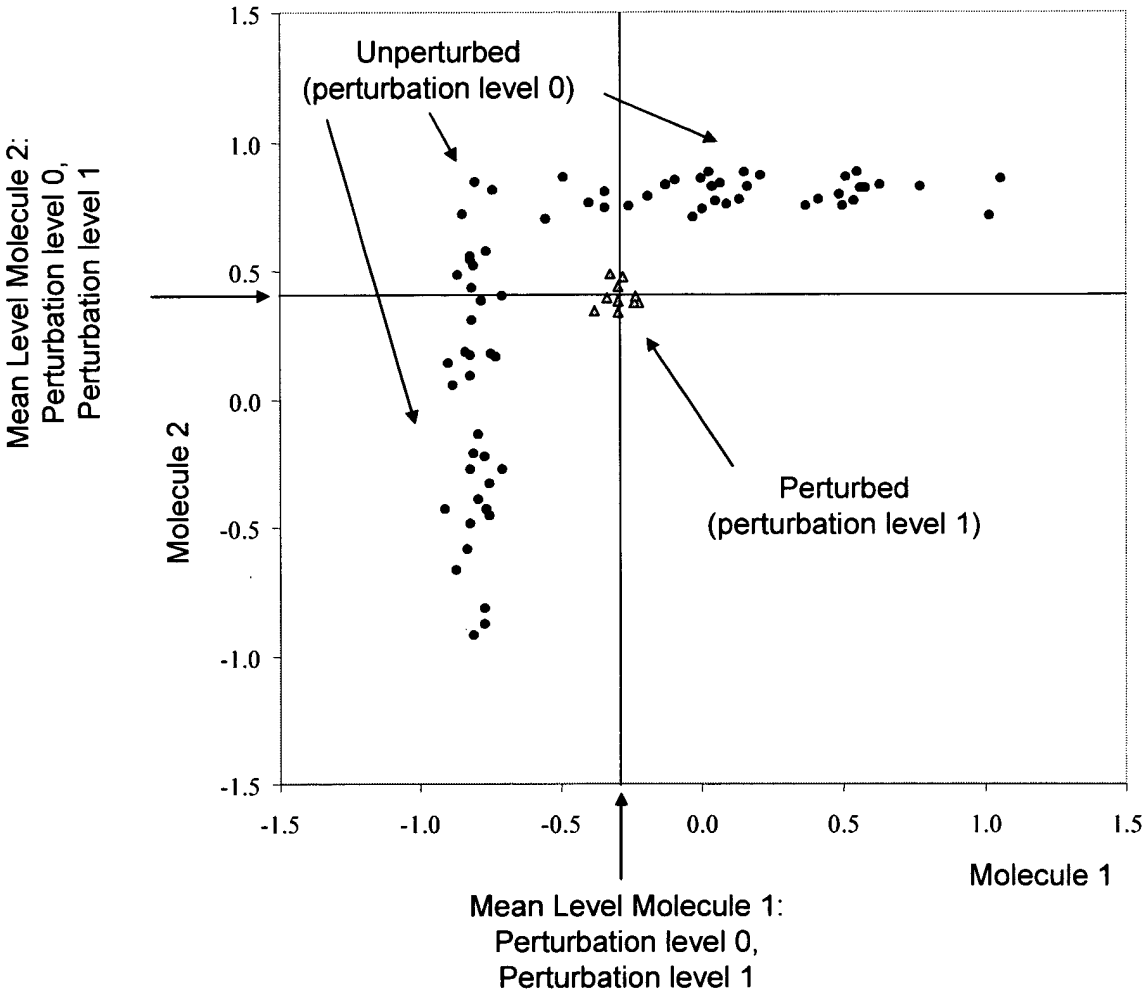
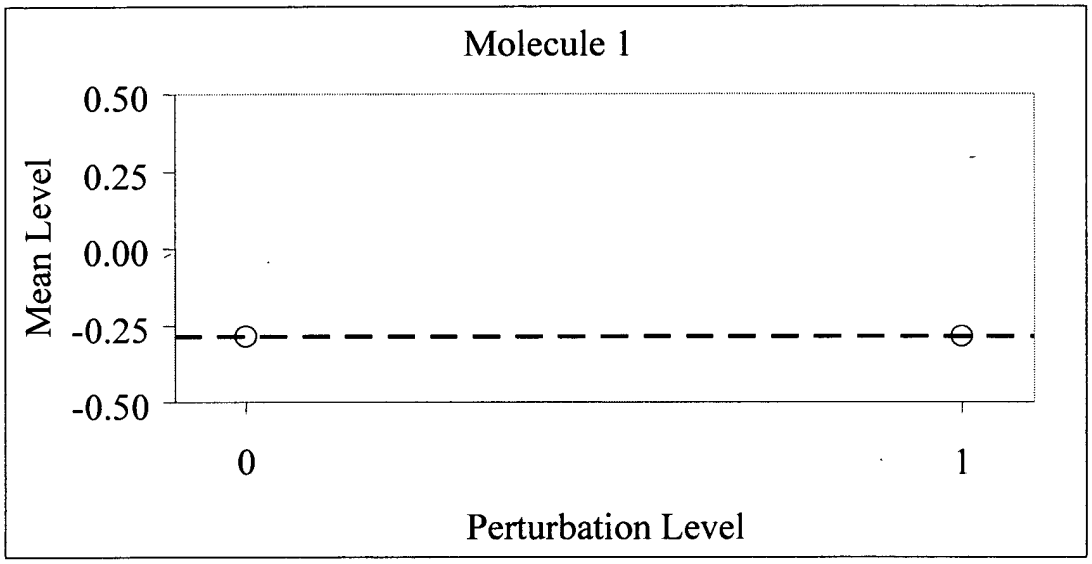
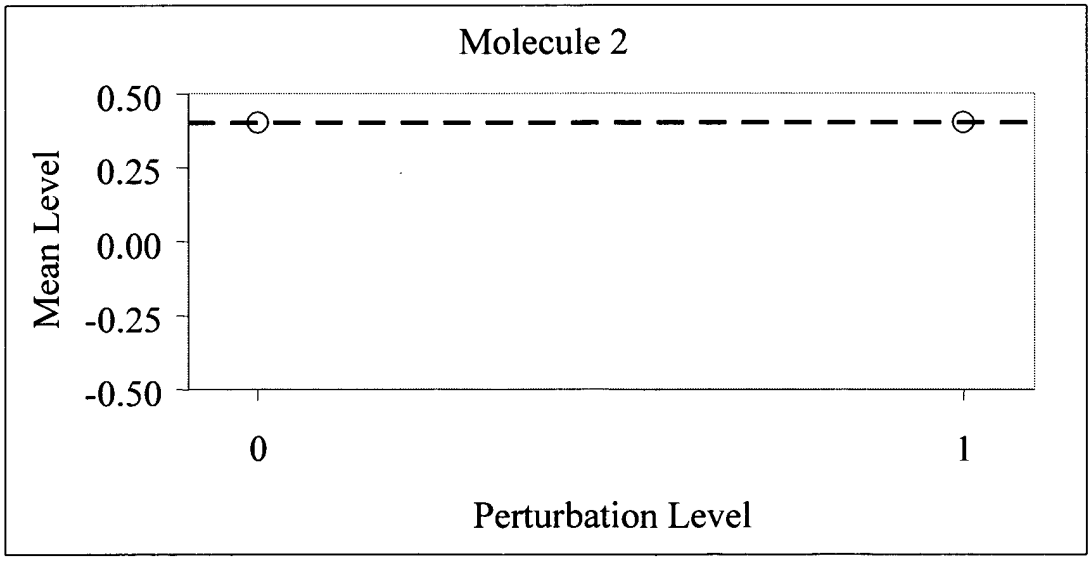


Exhibit B


Molecule 1
0.50
0.25
0.00
-0.25
-0.50
Mean Level
0
1
Perturbation Level


Molecule 2
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0.00
-0.25
-0.50
Mean Level
0
1
Perturbation Level